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Anxiogenic Properties of Yohimbine

II. Influence of Experimental Set and Setting

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Summary. To study the pharmacological induction of stress along with psychological stress and their possible interaction, 20 mg yohimbine and placebo orally were administered to 8 panic patients on placebo treatment, 7 panic patients on alprazolam treatment and 12 controls in a double-blind crossover design. Two structured situations which can be considered as 'neutral' stressors were included: a mental arithmetic task and a continuous performance task. Mental arithmetic induced robust increases in ratings of panicky, anxiety, nervousness, heart rate and electrodermal activity, while the continuous performance task induced increases exclusively in skin conductance reaction. Patients responded to these tasks less than controls with regard to subjective ratings and electrodermal activity. Yohimbine did not potentiate the response to the tasks in the patients. In controls, heart rate during the mental arithmetic task, but not during rest, was increased after yohimbine. In contrast to other yohimbine challenge studies no panic attacks were observed. It is hypothesized that the experimental design together with an instructional set that reduces expectancy factors and the inclusion of structured and time-limited tasks in a challenge paradigm is able to reduce the anxiogenic effects of yohimbine.

Key words: Electrodermal activity – Heart rate – Panic disorder – Stress exposure – Yohimbine

Introduction

In recent years interest has been focused mainly on biological aspects of panic disorder (Rachman et al. 1988; Teicher 1988; Uhde and Tancer 1990). However, biological models of anxiety require broadening, since there is an increasing body of evidence that anxiety responses of anxiety prone subjects can be modified by psychological factors and the experimental setting. Proponents of a cognitive theory of panic attacks (van den Hout and Griez 1982; Clark 1986) reported that the affective response to hyperventilation and CO_2 inhalation was determined by cognitive factors such as expectation and the recall of previous experiences with the induced sensations. Moreover, internal cues, including bodily sensations that are interpreted as dangerous, are likely to trigger panic attacks (Margraf et al. 1986). This is supported by reports that bodily sensations are one of the first things which subjects notice during an attack (Hibbert 1984; Ley 1985, 1987). Anxiety patients are more aware of bodily functioning (Tyrer et al. 1980) and body sensations are particularly likely to be noticed when there is a change in biological processes (Clark 1986).

Thus there is considerable evidence that attention to drug induced bodily changes might enhance the likelihood of experiencing a panic attack in anxiety prone subjects. Most challenge paradigms have facilitated concentration on bodily sensations by instructing the subjects to wait for the expected anxiogenic effects of a challenge compound. Until now only one study included a structured situation (isometric exercise) in a challenge paradigm (Nesse et al. 1984). The authors reported no occurrence of panic attacks in panic patients after isoproterenol application. In an attempt to minimize concentration on bodily sensations, our study included situations that subjects were required to cope with actively and which were intended to distract them from changes in physiological functioning induced by the challenge drug.

Previous stress research emphazises that different structured situations elicit different response patterns (Lacey 1967; Dimsdale and Moss 1980; Ward et al. 1983; Albus et al. 1986, 1987, 1990). A mental arithmetic task requires specific mental activation under social stress and is thought to induce a sensory rejection response (Lacey 1967) with increases in heart rate and electrodermal activity (Lacey 1967; Forsman and Lindblat 1983; Albus et al. 1986, 1988a, 1990). In contrast, a situation requiring concentration on external stimuli like a continuous performance task induces an orienting response with no changes in cardiovascular parameters (Lawler 1980; Erdmann et al. 1984; Spinks and Siddle 1985). Both tasks can be considered as "neutral" stressors with-

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out specific threat for clinically anxious subjects (Mathews et al. 1990). Previous investigations (Albus et al. 1988a, b) have found that such neutral stressors do not induce more pronounced physiological responses in panic patients than in healthy controls. Zucker et al. (1989) applied a mental arithmetic task and demonstrated that the cognitions of fear patients reported before panic attacks were not the same as those in anticipation of the stressor. The authors concluded that stressors like mental arithmetic produce non stress-related physiological changes which override whatever effect cognitions have in producing physiological changes leading to a panic attack.

As described in a companion article (Albus et al., this issue) our aim was to decrease the likelihood that patients develop panic attacks by the type of the experimental design and instructional set and by the inclusion of structured situations. This has never been done in challenge studies which assumed pure biological mechanisms for panic anxiety. Two tasks (mental arithmetic (MA) and continuous performance task (CPT) were added to a yohimbine challenge paradigm to answer the following questions:

1. After yohimbine administration do patients develop similar or different response patterns compared to controls to the two different tasks?
2. Does yohimbine influence task performance differentially in patients and controls?
3. Does anticipation of and actively coping with the tasks lower the incidence of panic attacks by preventing the patients from attending to yohimbine induced bodily changes?

Methods

Subjects

Controls were 8 females and 4 males with a mean age of 34.5 years. Patients (4 males, 11 females) met DSM-III criteria for agoraphobia with panic attacks or for panic disorder without concomitant depression (APA, 1980). Eight patients were under placebo medication for at least 2 weeks prior study, seven patients were treated with alprazolam over a period of 6 to 8 weeks and were under a stable alprazolam dosage for at least 1 week prior study. For details see Albus et al., this issue.

Apparatus

Physiological recording was done on a Grass polygraph (Model 7B), the output of which was digitized by a PDP 11/10 computer. Electrodermal activity was recorded from the distal phalanges of the middle and ring fingers of each hand. Heart rate was recorded by a Grass tachograph from an EKG signal. For details see Albus et al., this issue.

Procedure

All subjects participated in two test days during which they were randomly assigned to either 4 tablets of placebo or 4 tablets of 5 mg yohimbine on the first day and the opposite substance on the second testday. The interval between test days ranged from 1 to 3 weeks.

- 90 (min.)	Arrive at Laboratory	
- 60	Mood-Scale, VAS, STAI-X1, ZUNG	——i.v.
- 30		——NE
- 20		——NE, CORT
	3 min. Rest	
	1 min. Instruction	
	3 min. Mental arithmetic	
- 11	VAS, Mood-Scale	
	3 min. Rest	
	1 min. Instruction	
- 3	4 min. Continuous performance task (CPT)	
	3 min. Rest	
+ 0	**Yohimbin/Placebo**	
+ 75	Mood-Scale, VAS, STAI-X1	
+ 90		——NE, CORT
	3 min. Rest	
	1 min. Instruction	
	3 min. Mental arithmetic	
+ 99	VAS, Mood-Scale	
	3 min. Rest	
	1 min. Instruction	
	4 min. Continuous performance task (CPT)	
+110	3 min. Rest	

Fig. 1. Flow sheet for the yohimbine procedure

Structured Tasks

Mental Arithmetic Task (MA): Subjects subtracted 7 continuously starting from 500 (before tablet intake) or 13 starting from 1000 (after tablet intake) until they reached 0. If they made a mistake they had to start from the beginning again. Performance was evaluated in terms of number of restarts and the lowest correct number reached.

Continuous Performance Task (CPT, Rosvold et al., 1956): Letters were displayed one at a time for 0.5 s duration with a 0.7 s interstimulus interval. The subject's task was to press a button after an 'X' only when it had been preceded by an 'A'. Critical stimuli occurred randomly on 20% of the trials. Responses to X preceded by any letter but 'A' or responses to any other letter were considered errors of commission. If a response was later than the interstimulus interval it was considered late. Performance was evaluated by number of omissions, commission errors, and late responses.

The flow-sheet for the yohimbine procedure can been seen in Fig. 1

Blood was sampled for norepinephrine (NE) and cortisol (COR). These data are reported in a companion paper (Albus et al., this issue). Physiological recordings were done during baseline conditions (= rest) and the stressors mental arithmetic (MA) and continuous performance task (CPT).

Behavioral ratings were administered 35 minutes before and 75 min following the yohimbine or placebo dose, as well as after mental arithmetic. A visual analogue scale completed by the subject was used to evaluate the changes of 16 different mood states (e.g. alert versus drowsy, troubled versus tranquil, happy versus sad, tense versus relaxed, lethargic versus energetic). The subjects also completed an analogue scale for anxiety to measure the change of 5 different symptoms related to anxiety (panicky feelings, anxiety, nervousness, apprehension, muscle tension). Both scales were scored in 100 mm. The subject had to make a perpendicular mark at the point corresponding to his feelings at that time. Therefore, the score could range from 0 (not at all) to 100 (extremely).

Data Reduction

Analogue ANS data were digitized and stored on line for later editing and analysis by computer as described by Zahn et al. (1986). For details see Albus et al., this issue.

Data Analysis

The effects of yohimbine on physiological measures and subjective ratings were initially evaluated using analyses of variance (ANOVA) with independent dimensions of groups (controls, patients taking alprazolam, patients taking placebo) and order (yohimbine or placebo on the first test day) and repeated measures dimensions of drug (yohimbine or placebo), time (predrug versus postdrug), and condition (rest and task periods). The Huynh-Feldt epsilon correction for the degrees of freedom in repeated-measures ANOVAs was used. We report variations among conditions in this paper.

Results

Subjective Ratings

Condition Effects

The mental arithmetic task induced a robust increase in self rated panicky, anxiety and nervousness. However, there were no significant group differences in this (see Table 2). After mental arithmetic all groups rated an increase in apprehension (df 1; 24; $F = 7.43$, $P < 0.01$) and muscle tension ($F = 12.63$, $P < 0.001$) and rated themselves as more excited ($F = 28.57$, $P < 0.001$), discontent ($F = 19.52$, $P < 0.001$), troubled ($F = 14.65$, $P < 0.001$), tense ($F = 24.02$, $P < 0.001$), incompetent ($F = 12.31$, $P < 0.001$) and antagonistic ($F = 13.26$, $P < 0.001$) compared with rest periods, again without significant differences between the groups.

Yohimbine Effects

Yohimbine did not induce a more pronounced increase in any subjective rating due to the mental arithmetic task, in either the patient groups or in the controls.

Performance

Patients and controls did not differ in the lowest number or on number of restarts in the mental arithmetic tasks. Also, in CPT there were no group differences and no yohimbine effects on late answers, or on omission or commission errors. Thus, yohimbine had no negative influence on performance in MA and CPT in any of the three groups investigated.

Heart Rate Parameters (Fig. 2)

Condition Effects

There were significant increases in maximum heart rate (HR), mean HR, low HR, SD mean HR and SD high HR in all three groups in the MA task but not in the CPT. There were no differences between the groups in any of these (no significant interaction condition × group, see Table 2).

Yohimbine Effects

Yohimbine did not have significantly different effects on rest and task periods for the three groups as a whole (i.e. no drug × time × conditions effects). However, there were significant D × T × C × group interactions for mean HR and for low HR (Table 2). ANOVAs for the patients and controls separately showed that there were significant D × T × C interactions for mean HR, low HR, and high HR (all $P < 0.03$) for the controls but no

Table 1. Effect of the mental arithmetic task on self-rated panicky feelings, anxiety and nervousness in controls (n = 12), patients under placebo (Plac. Pat., n = 8) and patients under alprazolam medication (Alpraz. Pat., n = 7)

			Controls		Plac. Pat.		Alpraz. Pat.	
			Placebo	Yohimbine	Placebo	Yohimbine	Placebo	Yohimbine
Panicky								
Rest	pre	−60	2.8 ± 2	5.0 ± 4	31.6 ± 24	25.6 ± 21	20.7 ± 23	8.2 ± 4
MA	pre	−11	18.5 ± 29	21.7 ± 21	34.8 ± 20	25.3 ± 23	30.3 ± 31	12.4 ± 12
Rest	post	+75	9.5 ± 12	9.2 ± 8	15.3 ± 18	33.5 ± 24	15.2 ± 15	29.2 ± 34
MA	post	+99	18.6 ± 23	19.3 ± 29	30.5 ± 21	40.3 ± 33	29.3 ± 36	35.4 ± 35
Anxiety								
Rest	pre	−60	7.0 ± 6	8.3 ± 8	45.3 ± 24	34.3 ± 28	31.1 ± 30	24.1 ± 24
MA	pre	−11	25.1 ± 24	20.6 ± 22	51.1 ± 18	30.7 ± 21	40.0 ± 36	36.4 ± 25
Rest	post	+75	10.1 ± 13	10.4 ± 9	24.6 ± 20	40.2 ± 27	18.8 ± 18	34.0 ± 35
MA	post	+99	21.3 ± 21	18.5 ± 26	34.1 ± 21	42.1 ± 27	31.8 ± 34	46.5 ± 39
Nervousness								
Rest	pre	−60	5.9 ± 3	7.4 ± 7	45.6 ± 24	30.7 ± 19	33.2 ± 34	29.7 ± 23
MA	pre	−11	30.6 ± 25	24.7 ± 18	53.4 ± 20	36.3 ± 26	39.2 ± 35	43.4 ± 24
Rest	post	+75	8.9 ± 10	15.2 ± 11	21.8 ± 21	36.4 ± 22	21.4 ± 21	30.1 ± 30
MA	post	+99	24.5 ± 22	23.9 ± 25	35.1 ± 21	45.7 ± 26	33.7 ± 34	52.3 ± 34

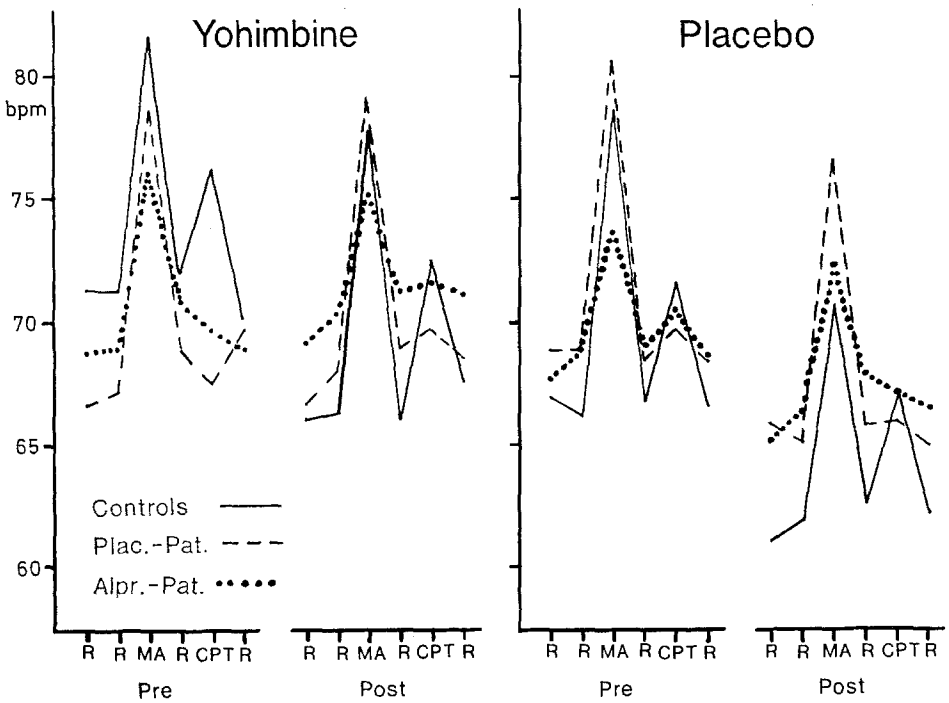

Fig. 2. Mean heart rate during rest periods (R), mental arithmetic (MA) and continuous performance task (CPT) before (Pre) and after (Post) yohimbine and placebo intake

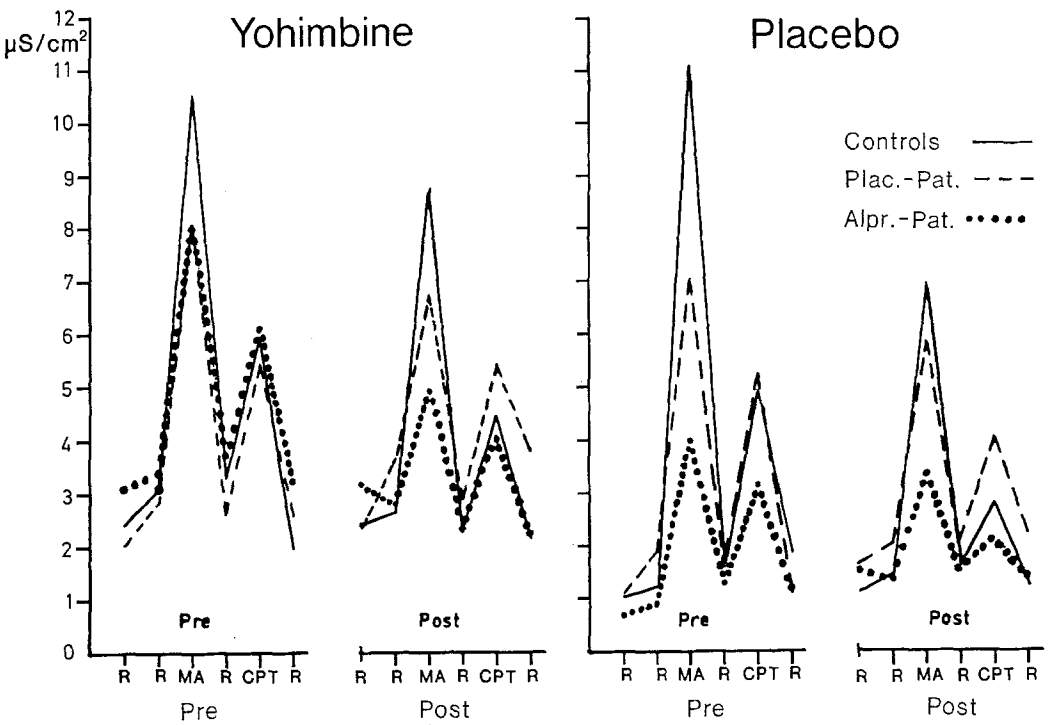

Fig. 3. Nonspecific fluctuations (NS/min) of skin conductance reaction during rest periods (R), mental arithmetic (MA) and continuous performance task (CPT) before (Pre) and after (Post) yohimbine and placebo intake

interactions for the patients as a whole or no interactions of these factors with medication. Examination of the data shows that the controls had a marked reduction in HR during the MA task from predrug to postdrug on placebo sessions, but this was strongly attenuated after yohimbine. This contrasts with virtually no difference between placebo and yohimbine sessions for the controls during the rest or CPT periods. The patients as a whole showed about the same effects of yohimbine during all periods.

Electrodermal Activity

Condition Effects

Both stressors induced a significant increase in nonspecific fluctuations (NS/min) of the skin conductance reaction (SCR). Only MA, however, induced a significant increase in maximum and mean skin conductance level (SCL). The stressor effects were more pronounced in the control group (significant interaction condition ×

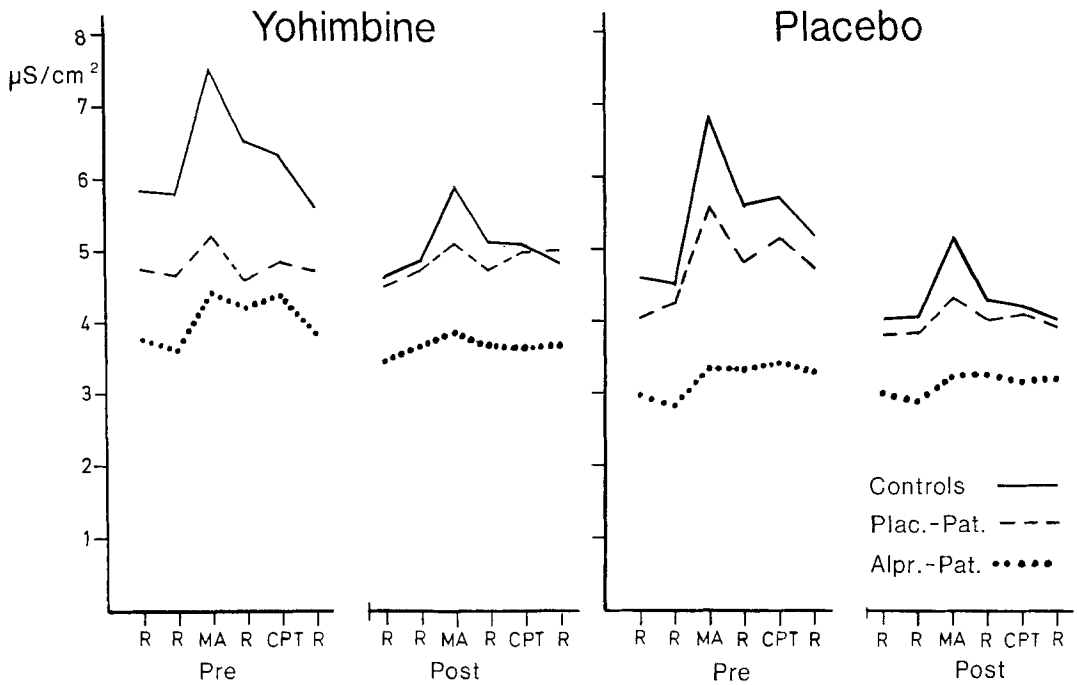

Fig. 4. Mean skin conductance level (SCL) during rest periods (R), mental arithmetic (MA) and continuous performance task (CPT) before (Pre) and after (Post) yohimbine and placebo intake

Table 2. ANOVA summaries

	Condition (*df* 5; 120)		Cond × group (*df* 10; 120)		Drug × time × cond × group (*df* 10; 105)	
	F	*P*	*F*	*P*	*F*	*P*
Maximum SCL	22.79	0.001	2.88	0.05		
Mean SCL	17.80	0.001	3.44	0.01		
NS/min	51.77	0.001	3.73	0.01		
Low heart rate	24.49	0.001			2.03	0.05
Mean heart rate	29.92	0.001			2.12	0.05
Maximum heart rate	36.51	0.001				
	df 1; 24					
Panicky	8.11	0.01				
Anxiety	8.39	0.01				
Nervousness	13.96	0.001				

group, see Table 2). However, the rate of increase (slope) in SCL during the instructions of both tasks showed a significant group effect ($P < 0.02$). This was slower in the patients than in controls,

Yohimbine Effects

There were no effects of yohimbine on the electrodermal responses to the tasks for the subjects as a whole or for any of the subgroups.

Discussion

The mental arithmetic task induced large increases in heart rate, the frequency of skin conductance responses, and skin conductance level. This finding is in concordance with the results of other studies (Ward et al. 1983; Albus et al. 1986, 1987, 1988a, 1990), showing that this situation evokes robust changes in physiological functioning. In contrast, the continuous performance task (CPT) led to a moderate increase exclusively in the frequency of SCRs. This finding is in line with other studies (Lawler, 1980; Erdmann et al. 1984; Spinks and Siddle 1985) and supports the assumption that a situation requiring concentration on external stimuli induces an orienting response with no relevant changes in cardiovascular parameters.

Like other studies comparing stress responses of panic patients with healthy controls without additional drug challenge (Albus et al. 1988a, b) our data show that panic patients respond to stressors which are demanding but not specifically anxiety inducing comparably to controls. Considering the even less pronounced increase in electrodermal activity in the mental arithmetic task in the patient groups one could conclude that panic patients are less challenged by the demanding characteristics of the task compared with healthy controls. Nonsignificant trends in the same direction were found for ratings of panic, anxiety and nervousness. However,

patients had higher base levels in subjective ratings. This ceiling effect may have suppressed further increases due to additional stress exposure. This finding shows that the law of initial values (Wilder 1957), that is, that the higher the prestimulus level the smaller is the response to function raising, is a valid concept (Yeragani et al. 1990) which may be important in psychiatric research. Since base levels in the parameters of electrodermal activity were not higher in patients than in controls, the law of initial values does not account for the less pronounced increases in SCR and SCL in panic patients. Therefore one can assume that panic patients are less responsive in electrodermal activity to external stimulation than healthy controls. In contrast, heart rate responses to MA were about the same in all groups. Both these findings are in agreement with earlier studies (Albus et al. 1987, 1988a, b) and reflect an overall reduced responsiveness to neutral stressors in panic patients.

Turning now to the influence of yohimbine on responses to tasks and task performance, the more pronounced overall yohimbine effects in panic patients (see companion paper, this issue) is also reflected in about equally more pronounced increases in heart rate parameters during MA and CPT in both patient groups after yohimbine administration. In contrast, the controls, who showed no effects of yohimbine of HR parameters under resting conditions, did show yohimbine effects on mean, high, and low HR during the MA task. Thus, during psychological stress, the controls showed effects of the drug that were shown by the patients under resting and stress conditions. Since yohimbine blocks the inhibitory alpha-2-receptors, this suggests that the HR of controls is significantly under adrenergic control only during stress periods, whereas the HR of the patients, despite its relatively low resting levels in the present study, is mainly under adrenergic control during even rest periods. This may account for the core position of changes in cardiovascular activity in the development of panic anxiety (Tyrer et al. 1980; Taylor et al. 1986; Ley 1987; Woods et al. 1987). However, yohimbine effects on the autonomic variables were smaller than condition effects for all groups. In agreement with Zucker et al. (1990) our data support the hypothesis that stressor effects caused by the characteristics of the task override yohimbine effects per se.

In contrast to studies that showed that anxiety patients do worse in tasks with anxiety specific threat (Ehlers et al. 1988; Mathews et al. 1990), panic patients performed as well as controls in both tasks. In spite of exerting overall more pronounced effects especially on heart rate parameters, yohimbine did not worsen performance in the patient groups. Thus, tasks that require mental activation or concentration on external stimuli may prevent patients from being disturbed by yohimbine-induced changes in physiological functioning.

Other research groups (van den Hout and Griez 1982; Hibbert 1984; Ley 1985, 1987; Margraf et al. 1986; Clark 1986; Salkovskis and Clark 1990) showed that induced bodily sensations that are interpreted as dangerous are likely to trigger panic attacks. Our data point to the necessity of distinguishing bodily sensations which are induced by a challenge drug from those induced by structured situations that allow active coping mechanisms. Although anticipation of the task and task performance induced a more pronounced increase in autonomic activity than yohimbine per se, patients did not develop panic attacks. In contrast to other yohimbine challenge studies (Uhde et al. 1984, Charney et al. 1984, 1987) no panic attacks were observed in the present investigation. Thus, tasks that patients can cope with actively seem to prevent patients from developing panic attacks by distracting them from focusing on drug-induced bodily changes.

Our results suggest that an experimental design together with an instructional set that reduces expectancy factors and physiological base levels as well as the inclusion of structured and time-limited tasks, in contrast to loosely structured challenge protocols, are able to reduce the panicogenic effects of yohimbine.

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